II. REMARKS

Preliminary Remarks –

Upon entry of this amendment, claims 11 to 14 will be pending, of which claim 11 is independent. Claims 1 to 10 are canceled and replaced by claims 11 to 14. Support for the new claims can be found in the specification and claims as originally filed (see, for example, page 34, lines 12 to 22). Therefore, the applicant believes that no new matter is added.

This response is filed within the statutory period for response and is accompanied by a petition for a 2-month extension of time and a check in the amount of the required fees for a small entity. The applicant respectfully requests consideration and allowance of the present application.

Election –

In the Restriction/Election Requirement, the examiner permitted the applicant to identify and elect specific embodiments not listed in the exemplary groups. Therefore, the applicant hereby elects:

Compounds of formula (I), wherein

s is 2,

b0 is 1,

A is an anti-inflammatory drug,

B is an aminoacid (*i.e.*, PI, PII, PIII, PIV, PV),

C is $-T_C$-Y–, wherein

T_C is O and

Y is Y_O, wherein

Y_O is R'O and

R' is a linear or branched C_1-C_{20}.

New claims 11 to 14 read on the elected species. Support for the elected group can be found in the application as filed (the examples, in particular, examples 1 to 4 and 8 relate to derivatives of anti-inflammatory drugs, and the claims as filed):

- Example 1 relates to a nitrooxy derivative of formula (I) wherein A is flurbiprofen, B

is (L) 4-thiazolidin carboxylic acid (PIV) and R' is linear C_4;

- Example 2 relates to a nitrooxy derivative of formula (I) wherein A is naproxen, B is (L) 4-thiazolidin carboxylic acid (PIV) and R' is linear C_4;
- Example 3 relates to a nitrooxy derivative of formula (I) wherein A is naproxen, B is (R) 2-oxothiazolidin carboxylic acid (PV) and R' is linear C_4;
- Example 4 relates to a nitrooxy derivative of formula (I) wherein A is diclofenac, B is (L) histidine (PII) and R' is linear C_4; and
- Example 8 relates to a nitrooxy derivative of formula (I) wherein A is cetylsalicylic acid, B is (R) 2-oxothiazolidin carboxylic acid (PV) and R' is linear C_4.

This election is made with traverse.

Reasons for Traversal –

In response to the examiner's objection of lack of unity based on the consideration that "the compounds defined in the claim lack a significant structural element qualifying the special technical feature that defines a contribution over the prior art" (item 2, page 4, of the Restriction/Election Requirement), the applicant would like to point out that the problem solved by the present invention is to provide compounds to be used in pathological conditions associated with oxidative stress and/or endothelial dysfunctions since, when a pathological condition is associated with oxidative stress and/or endothelial dysfunction, the known drugs show a lower activity and/or higher toxicity (specification as filed, page 2, line 25, and page 3, lines 1 to 2).

The above problem has been solved by the compounds of the present invention which are nitroxyderivatives of known drugs characterized in that the nitrate ester (*i.e.*, $-ONO_2$) is bound to the parent drug (the part "A" of formula (I) A-(B)-C-NO_2) via an "antioxidant" linker (the part "B" of the formula (I) chosen from a selected group of molecules having antioxidant properties).

The linking up of these antioxidant linkers plus the $-NO_2$ group to the known drugs represents the technical features characterizing the compounds of the invention, because it makes the obtained nitroxyderivatives efficacious and well tolerated in the

treatment of pathological conditions associated with oxidative stress and/or endothelial dysfunction.

As reported in the examples F5 and F7 (pages 86 to 88 and 102 of WO 00/61541) and in Tsables VI and VII (pages 108 and 109 of WO 00/61541), which refer to the evaluation of the gastric tolerability of the compounds of the invention in condition of oxidative stress, the presence of the antioxidant linkers plus the $-NO_2$ group allows to obtain an unexpected increased tolerability of the drug and, moreover, an unexpected gastric safety of the claimed compound in comparison with the gastric safety of a physical mixture comprising the parent drug and the antioxidant molecule or with the gastric safety of a physical mixture of a known nitroxyderivative of the parent drug and the antioxidant molecule (see Table VII).

As reported above, the results of the example F5 (see Table VI on page 108 of WO 00/61541) show that the diclofenac nitroxyderivative of example 4 has a high gastric tolerability in condition of oxidative stress, and the results of the example F7 (see Table VII on page 109 of WO 00/61541) demonstrate that the flurbiprofen nitroxyderivative of example 1 has a better gastric tolerability in comparison with a physical mixture comprising the flurbiprofen and the antioxidant molecule or in comparison with a physical mixture comprising a known nitroxyderivative of the flurbiprofen (flurbiprofen-C_4-ONO_2) and the antioxidant molecule.

III. CONCLUSION

In view of the amendments and remarks above, the applicant respectfully submits that this application is in condition for allowance and requests favorable action thereon.

In the event this response is not timely filed, the applicant hereby petitions for an appropriate extension of time. The fee for this petition, along with any additional fees required with respect to this response, may be charged to Deposit Account No. 01-2300, referencing Attorney Docket No. 026220-00013.

Respectfully submitted,

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